REMARKS

Claims 2, 4-9, 12-21, 28, 34, 35 and 38 are pending in this application. Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

I. THE REJECTION UNDER 35 U.S.C. § 102 IS OVERCOME

Claims 2, 7-9, 12, 13, 20, 21, 28, 34, 35 and 38 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Peach *et al*. The rejection is traversed.

Claim 2, paragraph (i), requires modification of a V-like domain such that the size of a CDR loop structure, or part thereof, within the V-like domain is increased by at least 1 amino acid residue. Applicants maintain that Peach *et al* do not teach increasing the size of any CDR loop structure within a V-like domain of CTLA-4 or CD-28.

The specification defines "CDR loop structures" on page 5, lines 27-30 as polypeptide loop structures or regions like the complementarity determining regions in antibody V-domains. With regard to this definition, the Office Action states that "the broadest reasonable interpretation is assumed to encompass at least a structure comprising a CDR loop, e.g. the V-like domain of CD28 or CTLA-4." This interprets "CDR loop structure" to encompass an entire V-like domain.

Such an interpretation is completely inconsistent with the way the phrase "CDR loop structure" is used throughout the specification. For example, the specification clearly refers to CDR loop structures as being ***within*** V-like domains (see page 4, lines 18-19). Further, Example 1 provides clear examples of the generation of randomised sections of "CDR loop structures" (see page 19, lines 20-23). Example 3 teaches how to replace the "CDR-1 or CDR-3 loop structures" of CTLA-4 with the somatostatin polypeptide (see page 22, lines 24-25), and how to replace the "CDR-2 loop structure" of CTLA-4 with the haemagglutinin epitope (see page 23, lines 9-11). Example 4 teaches how to replace the "three CDR loop structures" of CTLA-4 with the three CDR loop regions from an anti-lysozyme antibody (see page 24, lines13-15), and Example 5 teaches how to replace the "three CDR loop structures" of CTLA-4 with the three CDR loop regions of an anti-melanoma antibody, V86 (see page 25, lines 4-5).

Thus, from a reading of the specification as a whole, it would be clear to a person skilled in the art that the phrase "CDR loop structure" refers specifically to "loop structures which are CDR-like" and not to "structures comprising CDR loops" as suggested by the Examiner. The

way in which the phrase "CDR loop structures" is used in the specification is entirely consistent with the interpretation that would be given by one of ordinary skill in the art at the time the invention was made. In particular, a skilled addressee would understand from a reading of the specification that a "CDR loop structure" would not include the buried beta sheet sequences forming the framework of the V-like domain.

Moreover, the claim language is clear. Claim 2 recites a "V-like domain **comprising** at least one CDR loop structure." Therefore, a V-like domain is not equivalent to a CDR loop structure; rather, it is a larger structure that contains a CDR loop structure. Applicants therefore submit that claim 2 clearly encompasses modifications of a V-like domain where the CDR loop structure itself (rather than a framework sequence) is increased in size by at least one amino acid.

Turning to Peach *et al*, it is submitted that this publication does not teach replacement of CDR loop structures with longer CDR loop structures. The Examiner relies in particular on the ligand HS3 depicted in Figure 3 of Peach *et al*. The Examiner states that creation of the ligand HS3 involves replacement of the region between conserved cysteines at positions 21 and 94 of CTLA-4 with the corresponding CD28 sequence, which is longer by one amino acid.

The Examiner appears to have misread the legend to Figure 3, interpreting the filled areas as CD28 sequence. In fact, the filled areas are CTLA-4 sequence. There is no replacement between positions 21 and 94 of the CTLA-4 sequence. This is further supported by Table 2 which indicates that HS3 is a variant based on CTLA-4, in which the only modification is a replacement at positions 97-126 of the CTLA-4 sequence by CD28 sequences.

The only CDR loop structure which is within or close to the CD28 sequence inserted into HS3 is the CDR3-like sequence which is defined by Peach *et al* as encompassing residues 97-104 inclusive as shown in Figure 1. The CDR3-like sequence (CDR analogous sequence) for CTLA-4 as defined in Figure 1 is ELMYPPPY. The equivalent sequence for CD28 is EVMYPPPY, however, based on the sequences provided in Table 2, it would appear that the CDR3 loop structure in HS3 did not include the L to V change, and that the CDR3-like sequence in HS3 is identical to that in the parent molecule CTLA-4. Thus, the replacement in mutant HS3 does not result in any change at all, including any increase in the size, to the CDR3-like sequence.

Peach *et al* in fact show no examples where a CDR-like loop has been replaced by a longer CDR-like loop. Figure 1 clearly shows that the CRD1-, CDR2- and CDR3- like loops of

CTLA-4 and CD28 have the same number of amino acids. Thus, for all mutants (i.e. HS1 - HS14), the number of amino acids in the CDR-like loops is the same as for the wild type (CTLA-4 or CD28) sequence. Therefore, Peach *et al* do not teach replacement of CDR loop structures with longer CDR loop structures, as is required by the language of the claims. As such, Peach *et al.* do not teach every element of the claims.

In view of the foregoing, reconsideration and withdrawal of the anticipation rejection are requested.

II. THE REJECTION UNDER 35 U.S.C. §103 IS OVERCOME

Claims 2, 4-6, 18 and 19 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Peach *et al.* in view of Koide. The rejection is traversed.

The comments above concerning Peach *et al* are reiterated and added to the following comments concerning the Koide reference.

First, a person skilled in the art would not look to the Koide reference as being relevant to the issue of modification of CDR loop structures within V-like domains such as CTLA-4, CD28 and ICOS. Koide describes Fn3 domains from fibronectin as being highly variable molecules with a large degree of natural variations in the BC and FG loops, and notes that there are seventeen different Fn3 domains present in human fibronectin. This indicates a considerable degree of latitude in the sequences of these loops, while still allowing the protein domains to fold effectively. In contrast, the sequences of Figure 1 of Peach *et al* show the relatively tight evolutionary constraints on size, if not sequence, which have preserved the related protein structures of CTLA-4 and CD28. Thus it would not be apparent to one skilled in the art that a molecule such as CTLA-4 could accommodate increases in size in the CDR-like regions and retain its essential properties.

Further, the data presented in Koide on fibronectin shows that the FG loop which is naturally long and variable, does not contribute significantly to folding, or stability of the overall protein and the FG loop can be mutated extensively without affecting these parameters. In contrast, many of the variants of CTLA-4 exemplified in the present specification (some of which had increased size in the CDR-like sequences) show increased stability and/or solubility, suggesting much less latitude for change within the CDR-like regions of these molecules before properties dependent on the overall structure are affected. Thus, a person skilled in the art would

not be motivated to combine the teachings of Koide, which relate to Fn3 domains, with those of Peach *et al* which are restricted to the V-like domains CD28 and CTLA-4.

Further, as explained in the previous response, all the examples in Koide teach replacement or deletion of residues. In particular, Koide suggests that shorter CDR-like loops may offer advantages (see paragraphs 66 and 200) and indeed it is a clone ("Ubi4") containing three deletions in the FG loop which was the most successful in achieving a desired property, presumably retaining appropriate folding and stability of the underlying protein (see paragraph 203). Therefore, the skilled person would have no reasonable expectation of success in, for example, improving the binding affinity, as a result of increasing the size of a loop structure based on the teaching of Koide.

In conclusion, the combined teachings of Peach *et al* and Koide *et al* do not in any way suggest modifications of CDR loop structures within CTLA-4, CD28 or ICOS which involve increasing the size of a CDR loop structure by at least one amino acid residue. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are requested.

CONCLUSION

In view of these remarks, the application is in condition for allowance, or at least in better condition for appeal. Entry of this paper, favorable reconsideration of the application, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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